DIVISION OF LIFE SCIENCES OFFICE OF SCIENCE AND TECHNOLOGY
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH FOOD AND DRUG ADMINISTRATION
5600 Fishers Lane
Rockville, Maryland 20857

MEETING: Epidemiology Research Needs Related to the Radio Frequency Energy From Wireless Phones
PLACE: The Regal Cincinnati Hotel
Cincinnati, Ohio

DATE: April 19th, 2001

ATTENDEES: Russell Owen, Ph.D. Abiy Desta
Quirino Balzano, Ph.D. Mary McBride, M.Sc. John Moulder, Ph.D. William Lotz, Ph.D.
Barbara Grajewski, Ph.D.

P R O C E E D I N G S

8:30 a.m. DR. OWEN:

Thank you for coming. I just got a message Barb saying that she was going to be a little late.

Yesterday was real helpful and then we lost a couple people overnight, but we are still trying to get a little more accomplished this morning.

I plan on being done by 11:00. We will probably sometime between now and then, have a real short break, so people can take care of whatever they need to take care of. I want to spend this morning going back over some of what we talked about some of what we talked about yesterday for clarification and extension of any points that came up. I got part way through organizing my notes to get things started and we'll see. I will need more help the further we go along.

Just to back up and remind people of the context of this meeting, as part of the FDA/CTIA Cooperative Research Agreement on wireless phone RF exposures, the scope of that in general is animal, cellular and human studies -- pretty much everything needs to be looked at one way or another.

Of course, FDA's role in this is to

provide the scientific advice. Our present task for FDA is to consider what follow-up is needed for the Muscat et al case control study that was funded by CTIA and published in December. At this stage, we are using different methods to gather expert scientific input and this meeting is part of that. It's the first of two scheduled meetings.

Now, I would like to start with what I just said. What follow-up is need for Muscat et al? I tried to list out some of the data gaps that we discussed and the types of remedies that might address those data gaps.

I don't have things in a particular order here, because I didn't spend a lot of time on it. Maybe I should quickly go through this whole table and then we can pop back to the beginning just so you can get an idea of the kind of organization we would like to have to the discussion -- nothing hard and fast, of course.

So, you see under induction time, which is one of the easiest to identify data gaps in the case control studies since we, by requirement of when the technology became available in wide use -- has been limited. The IARC collection of studies -- and I say as is, meaning in the absence of adding additional

participants to that collection of studies, the US one, for instance. We will do something to address that issue.

I also put in there that animal work -and when I talk about animal work here, I just made a note, that I mean also human laboratory studies where it makes sense, not necessarily for this part, but later on down. Animal work has the strong potential for looking at long induction time health effects with all the caveats that are inherent in using animal studies to inform assessments of effects on humans.

We also mentioned the potential of using high RF exposure populations to identify -- we talked about that both, I think, in terms of case controls and in cohorts, so I just threw some of those down here.

Of course, cohort studies could also address long induction time questions and I noted there just for my own recollection, we talked mostly about new cohort studies that could be done in the US or elsewhere, but I also put down UK just to remind myself that we mentioned that we have got the UK research program that includes, at least in it's call for work, cohort studies. We don't know where that is going to go yet.

So, moving on to the next data gap entry

there, are there other outcomes that weren't looked at? By the nature of case control studies, you can only look at what you decided to look at before the do the study. Again, in the IARC collection of studies, there are I think going to be some look at other outcomes than the ones that we covered in the existing case control studies -- not very broadly, but some extension.

We mentioned a couple times the possibility of using disease registries, particularly for looking at diseases of stable incidence to identify other outcomes that may need study. And again, animal work has the potential for informing the need for looking at other outcomes.

Under sub-group finding -- all of this I have just kind of use a shorthand that I hope brings back what we talked about enough to everybody and this is not intended as a full description of anything. Of course, part of that, although not by design, was addressed by Peter Inskip in a study that is already published and I anticipate we could learn a little more on this from the IARC collection of studies.

There was also mention of doing some sort of pooled or parallel analysis of the data. It was discussed in two ways. One, of trying to somehow look

6 at the Inskip and Muscat data in some kind of fashion together. But I added comments there, because there was a lot of discussion of the fact that in this socalled or what I am calling a sub-group finding, a lot of people pointed out that it was actually not provocative. There were questions about classification, sub-groups of type -- what does that really mean and who is the one doing classification? The fact that we don't have biological mechanisms that are established that would support that particular subgroup finding or any other particular one at this point. Again, pointing back to the need for using laboratory studies to inform the design of epi studies.

And there was also a mention of the relatively small -- small relative risk that came out of this and how that might influence your decision on needing follow up a data gap like that.

Of course, exposure assessment is a giant question that can be considered part of follow-up for the Muscat study. It's a little bit less direct, but certainly is a critical need in terms of going forward in any studies and certainly cohort studies.

I tried to get just -- we had a lot of discussion not all that specific, but at the end of it, it seemed like what we

really need, and I look forward

 to hearing

more on this, is a fuller analysis of the relative impact of all the various parameters that in the end that affect the exposure or the tissue dose.

We talked about a lot of different ones. There is some knowledge -- a fair amount of knowledge of the individual parameters. It sounded like from yesterday's discussion that nobody has actually taken all of these together and figured out which one -- is there one that sort of swamps all the other ones and would be the most important to pay attention to. And that is going to be important, not only for the specific design of any future studies, but also just for the general assessment of any studies in having to do with this public exposure to RF. There really is a need, it appears, for a little better handle on all the exposure information.

Now, I left to the end --

DR. LOTZ: Russ, before you go on from there, I was going to say it seems like one of the things that we talked about yesterday -- I think maybe John particularly brought it up -- it's both a question of getting a comprehensive analysis of all the relative parameters or the relative impact of all the parameters, but it's also a problem in that we don't really have the bio-mechanism, biological mechanism

information to know what metric is the most critical.

DR. OWEN: I want to come back to that in the minute.

DR. MOULDER: That really is different than the exposure assessment he is raising.

DR. LOTZ: That's what I was -- that is why I brought it up. It's an additional issue. It doesn't take anything away from the importance of that, but it's an additional unknown or gap.

DR. OWEN: I am going to add that in a minute to that box.

DR. BALZANO: That gap might not go away any time soon, but that is why, again, in the exposure assessment done properly the way I would suggest to do it, you can actually sample the data in such a fashion. For example, you can find time up over a certain level.

DR. OWEN: Yeah.

DR. BALZANO: Okay, if that is the issue. And, for example, as was pointed out yesterday, is what is important 60 minutes at one time or 10 times six minutes? There are some people who actually feel that 10 six minutes is worse than 60 minutes in a row, in one shot.

Obviously we are dealing with exposures that are very difficult to put your hands around and

 this has been our affliction. Let's face it.

DR. MOULDER: But the day somebody does come up with a biological mechanism that suggests a metric, it's still going to need this exposure assessment data.

DR. BALZANO: Thank you. Thank you very much.

DR. OWEN: That is why I pulled it out as a separate piece from talking about cohorts and really sort of separate from anything else, because it really informs all of the studies. Because the goal of doing any of the epi or animal or cellular or any of this research, the reason all this is being done, is to in the end assess the impact of the human exposures.

DR. BALZANO: That is really what we don't have the good handle on because it's never been done properly. This might be an opportunity. The European IARC -- let me call it that -- has made a good first attempt. It was very timid. Epidemiologists are all pretty tied to their own traditional tools, like everybody. I am not trying to be in any fashion disparaging. Absolutely not.

But the technology should be utilized as much as possible. For example, Ken suggested they use the web. Forget about the paper. You test your paper,

 but you do your data collection to the web. These are the modernization of the epidemiology that we got to look forward to because I think that the animals are not going to tell us very much. The human experience over a period of time, if there is an issue, time will bring it up or shut it down. It's impossible to shut it down, but time will drive the issues.

Finally, epidemiology is our chance to do it right, in terms of predicting what might be an issue. But for that, epidemiology got to use the best tools available and more often that not, they still don't do that just because, again, they are set in a certain fashion.

So, along with the exposure, I would really suggest that we use -- after proper testing obviously -- as much as possible whatever the web can give us as a tool and also whatever information can be extracted directly from the phone, because the phone can be made at least in a phase of testing to give you the information directly. A certain time of the day, a phone can spew out a certain amount of information it has collected automatically during a phase of testing and validation.

At that point, since you are using an automatic testing system with a substantial amount of

data, you can extract all the parameters that later on you can use if necessary. If you are just tied down to a printed piece of paper instead of tables of data, your life is much more difficult.

DR. LUNDQUIST: Since we are talking about this -- let me tell you, I have another handout. I felt that some of the comments that were made after I made my presentation indicated I had not really gotten my point across as well as I should have. So, I have done it in writing and I'll put these at the head of the table for everybody.

DR. OWEN: Okay. Thank you. I do want to come back, but just want to finish the rough outline and then go back to the beginning of what I have here.

I just started listing, actually going first to my notes from the end of the day, a lot of the factors that we talked about with respect to a prospective cohort study.

But, before we go back to all of that, I wanted to go down a little further, the things that I have got higher up on the page here.

DR. BALZANO: There is one thing we forgot yesterday, very, very important. We forgot to put important parameters for cost.

DR. OWEN: Yeah, well --

BALZANO: Before we end the session, we should put somewhere a range of numbers to show that we have to be responsible for all our decisions.

DR. OWEN: I would appreciate and information you do have on that, but just to go back the to very beginning at 8:30, I am not expecting this group or this meeting to deal with logistical issues like the cost, like the legal environment and all those kinds of things. But, I would very much like to know what things would cost. I have got to know that at some point.

DR. BALZANO: In order to show responsibility, we got to show that we have an idea of what this is going to cost. Otherwise, it sounds like you are reaching for the pie in the sky. I agree with you on the legal aspects, it's none of our business, but at least to put the dollar value on what you are asking, is a sign of --

DR. McBRIDE: It may be difficult to see if we can do that. Certainly as an epidemiologist working in Canada, the way our costs work are completely different.

DR. BALZANO: Too bad Ken isn't here. DR. McBRIDE: He and Peter are not here and they would be the best.

Even Ken said at this point, he could only get within an order of magnitude, but believe me, I will be hammering him for that number.

DR. BALZANO: We should try to do that though, because otherwise it sounds like we are walking in mid air in the ozone instead of putting feet on that ground.

DR. OWEN: Thank you. Okay, back up to induction time -- and we don't have to recapitulate, of course, all the discussion we had yesterday, but what I really wanted to fish for here was anything that you think requires clarification from what was said yesterday or, even more importantly, extension of what was said yesterday in this sub-part.

DR. MOULDER: I think there is a piece of what was said yesterday that I don't see there and that was the feeling I think around this table that additional US case control studies are not -- we don't see any way that is going to help the induction time probably.

DR. OWEN: Yes, actually that was what I was trying to capture in the IARC studies as is, meaning not adding a US group.

DR. BALZANO: That would be one of the answers to Dr. Slessen's question. He asked a very

specific question. He said well, if you felt that as is is more than sufficient, we can tap into it. It's a perfectly good question and a perfectly good answer.

DR. McBRIDE: I am curious, Russ, as to what human studies you have thought of today specifically to look at induction time.

DR. OWEN: What I really meant with that notation was that further down -- I wrote animals studies on this table by inclusion. I meant humans as well. I meant human laboratory studies as well as animals, where appropriate. I don't think it fits specifically to induction time, but rather more to other outcomes.

DR. McBRIDE: Yes, other outcomes.

DR. MOULDER: I don't see where experimental human work is going to help answer any of the data gaps in the Muscat study. I don't see how it could help you with induction time or sub-group --

DR. OWEN: Well, it could address other outcomes clearly.

DR. MOULDER: Other non-cancer outcomes, yes.

DR. OWEN: Sure.

DR. BALZANO: I think it should be a little bit clearer --

 DR. MOULDER: Where animal work might address some of the cancer issues.

DR. McBRIDE: Yes, if you are looking at a pre-cursor --

DR. BALZANO: Especially if you are looking at laterality and the Muscat issue. It's very difficult with an animal.

DR. MOULDER: I agree. Maybe not going to give you laterality.

DR. BALZANO: Yes, that's right. The exposure just wouldn't make any sense.

DR. MOULDER: One place animal studies is going to help you is on induction time.

DR. OWEN: Could be a pre-cursor or bioeffect related to an outcome.

DR. McBRIDE: So that still fits in there. DR. BALZANO: I was under the impression that were pretty much talking about cancer.

DR. OWEN: I could use some help on the business of high RF populations with respect to case control studies, because as I said, I thought we had people mentioning that both in terms of possible cohorts, but as well as terms of case control, but I

put it there mostly to remind me that I need clarification.

MOULDER: I think for the emergency workers and the tower climbers, it almost has to be cohort, because they are sufficiently -- well, certainly tower climbers would have to be cohort, because they are a rare population. You are not very likely to happen to have any tower climbers in a case control study.

Even emergency workers are not a sufficiently common population that they would pop up in a case control study.

DR. McBRIDE: The difficulty of course, they are not too common a population and we are looking at a relatively rare outcome on brain tumors. You are not going to find it either --

DR. LOTZ: You can't assemble a big enough cohort.

DR. McBRIDE: No.

DR. MOULDER: I mean, miliary emergency workers might be big enough that you would hope to find something in a cohort study.

DR. McBRIDE: Yes.

DR. MOULDER: So, I would basically assume that the high RF population almost by definition have to be cohort studies.

DR. McBRIDE: I guess I am just saying

 some of those identified special populations you may not get any information from because the population size is too small.

DR. BALZANO: You have to identify first the population studies and the incidence and then decide.

DR. McBRIDE: Yes.

DR. OWEN: Good. Thanks.

DR. BALZANO: I mean, tower climbers, you are talking about relatively few people. There are also known tower climbers -- a lot of them, many of the sites now are not necessarily -- some of them are on towers, but some of them are on top of roofs.

DR. MOULDER: So, we really are talking antenna installers.

DR. BALZANO: I would like think in those terms. Probably that will expand to your antenna maintenance, site maintenance personnel.

DR. MOULDER: We are talking about buildings that have multiple providers on them, that actually provide some of the best, if you will pardon the expression, chance for exposures.

DR. LOTZ: Yes.

DR. BALZANO: But normally, though -- let me give

you a piece of caution on this -- if done

properly by suggested company approach, they are supposed to shut down the antenna to work on it.

DR. MOULDER: But you started out with if. DR. BALZANO: Yes, you should do that. DR. MOULDER: A very big if.

DR. BALZANO: They are very, very specific and they have a tag-out -- it is impossible to turn on the RF when the guys are there.

DR. MOULDER: They can control their antennas, but they cannot control the antennas belonging to other people.

DR. OWEN: That actually brings up an interesting point that maybe is not quite in the purview of our present discussion, but certainly in the bigger picture. What is the compliance in terms of that kind of recommendation.

DR. LOTZ: I was going to say, I have talked to Curtis about that some. Other than anecdotal information, which we know there are some cases where the system failed you might say, that there wasn't an adequate lock out or tag out. I don't know that we know very well -- and a part of the problem is this issue of multiple antennas belonging to different companies at the same site, so that it becomes a difficult matter.

 You go on the roof, okay, the antenna maybe they're initially concerned with, but there may be quite a few others there was well.

DR. OWEN: I can imagine it would be difficult information to collect because people don't want to incriminate themselves --

DR. LOTZ: And it becomes sort of a -it's not my problem because my individual source is fine, but when the worker goes up there, it might be a problem because collectively all the sources may --

DR. BALZANO: The sources are a certain distance from each. You have a grid with a minimum distance. First of all, the exposure even if the antenna is shut down and they are working properly -this is a good hypothesis -- you have enough from the lateral antennas, the one in the same grid, to give you a pretty good RF exposure and in that sense, this is interesting because you won't have a limited exposure. You would have the entire body exposure. That would be very interesting.

And on top of that, the dosimetry is not going to be very difficult either. If we could find -identify the population and the sites, this potentially could be a good study, because it is near exposure, the dosimetry can be done, -- it depends on how far they

 are, but you don't have the -- 100 to one changes that you get from the cellular telephone. You don't have the power necessary going up and down wildly and the positioning would change -- you can crouch, but meanwhile, you still have whole body exposure rather than one organ only.

DR. McBRIDE: I just wanted to ask you -I am thinking of this in terms of conducting a study, either a case control of a cohort study, if you are looking historically, you are talking about the site maintenance that is taking place over several years. I don't know if these workers go to different sites, whether the number of antennas on a site changes, how well that would be documented, so although it may be at the time one could get good dosimetry, how well can you get it in a historical context?

And again, in a cohort study, if we follow the model that has been suggested yesterday and get information every six months again, how well can we get self-reports of that kind of environment? Can we get information to get some measure of dose or is it all we can get --

DR. MOULDER: My guess is that you are going to end up a group of people, some of whom probably have had some high exposures and you are not

 going to get much better than that.

My question was -- ballpark, are we talking about a thousand people, 10,000, 500?

DR. BALZANO: No, no, more than a thousand.

DR. McBRIDE: I am thinking of occupational exposure with job title and then exposure yes or no and then --

DR. BALZANO: You are relying on the traditional methods at that point.

DR. McBRIDE: Yes.

DR. BALZANO: However, let me point out one thing. Normally, in order to make an installation you have to have FCC. You get at least the date of installation, so you have got some history, because these are all licensed equipment and I am sure the same thing as CADI, by the way. At least in terms of operation.

DR. LOTZ: A building permit at least. DR. BALZANO: You need something. You can't put a stick up there and start radiating. So, you should have some historical data or what happened to the site.

Now, could be very well that over time, they switched the antennas around. In other words, the

present antenna configuration might not be the historical antenna configuration, but that is no different than from any other study that you have done previously, in terms of what happened previously.

DR. McBRIDE: No, I am just pointing out and out and trying to think of it in terms of a study is all.

DR. LOTZ: I think the other thing, Mary, that makes it probably a difficult population is you are dealing with people who are not by employment tied to the site that you are looking at at all. They are independent contractors who come and go to different places and relatively kind of transient sort of work situation that -- because they are going around doing this on many, many different sites.

Even the air conditioning service man up on the roof where there is the antennas may or may not be anywhere connected employment-wise to who owns the site and that kind of thing, so it becomes I think probably much more labor-intensive to try and find the population.

DR. McBRIDE: So, transients geographically, but also longitudinally. I don't know how long people stay in that particular occupation compared to others. Anyway, so are just some of the

feasibility issues.

DR. BALZANO: But there are some advantages.

DR. McBRIDE: Mm-hmm.

DR. BALZANO: In the sense that you have whole body exposure --

DR. McBRIDE: And relatively high exposure.

DR. BALZANO: Yes, there are pluses and minuses everywhere.

DR. OWEN: I don't know whether I am going to get much extra comment on where I have got other outcomes here. I guess I should have put cohort on this one, too, as a possible way to address the question of other outcomes, because you can look at so many outcomes in cohort studies.

DR. MOULDER: Well, the other critical thing is that you don't strictly speaking have to decide in advance. Whereas, a case control study, you are locked in basically when you design it.

So, a particular advantage of a cohort study is as you think there may be other outcomes that you want to look at in the future, but you don't know what they are --

DR. OWEN: Yes.

DR. McBRIDE: So, animal work does include maybe some clinical studies or human lab studies that might look at as Peter described yesterday short term effects.

DR. OWEN: Yes. Since Q. mentioned the cost on cohorts, there were several comments about disease registry type studies, that it was inexpensive. What does that mean? What does inexpensive mean for a study like that, the simple, inexpensive disease registry type studies?

DR. McBRIDE: I have to think -- very low cost.

DR. BALZANO: Over 10,000, over 100,000? DR. McBRIDE: Not 10,000. I am thinking that along with the SEER registries, which cover about 14 to 15 percent of the US population, but is not representative in some demographic characteristics. Since 1992 when the US passed their disease registries -- I forget what it was called, but there is now a state registry in virtually all of the US states and they adhere to fairly stringent standards for data completeness and accuracy and those are all compiled annually. All the data is reported centrally through the North American Association of Central Cancer Registries.

25 I know --

let me back off here. It's not published yet. There is the potential through that network to look at national data on rare cancers, so the data is collected. There is a certain quality standard. It's fairly current.

DR. MOULDER: Is it computerized?

DR. McBRIDE: And it has 10-year trends for a lot of data, since 1992. So, it would be a matter of calculating statistics.

DR. BALZANO: So you are talking in the 10K range?

DR. McBRIDE: Yes, I say just calculating statistics when we want to do some clarification of the data and interpretation.

MS. BASILE: Excuse me. I don't know if this helps, but at one point someone gave an estimate of the National Death Index on an annual basis of about $200,000 for the data.

DR. OWEN: For the subscription to the data, yes.

MS. BASILE: I don't know if there is any correlation.

DR. MCBRIDE: It's a good question, JoAnne. In my experience with the NACCR data base, they have worked on a contract basis and basically on a

 cost-plus
basis. The National Death Index is usually - the studies that I have seen are linkage. I sit on the NACCR board, so I have some idea of what kinds of projects there are and I am thinking that it's different.

MS. BASILE: Well, that is the only data number I know, so I just thought I would throw it out.

DR. McBRIDE: Maybe there is something there I am missing, but I have seen it done.

DR. OWEN: That is very helpful.

DR. BALZANO: And of course, there are all the caveats that go with this so-called cheap and dirty study. If you remember, there were many caveats given to you about the significance of doing something --

DR. OWEN: Yes, yes.

DR. McBRIDE: And actually, just to add to that, the SEER data base is available through their website, plus the tools to do trend analysis of age standardized rates. I mean, anyone can go on and do it, as far as I know -- or maybe it's only licensed people. Whether it covers all rare cancers -- I know it covers -- I mean, the data all should be there.

DR. OWEN: Okay, back now to the one I have listed -- a sub-group finding. Maybe I can use a little help on clarifying the possibility to doing some

sort of pooled or parallel analysis with the data that are in hand. I think that Peter was the one who mentioned that, so I can get with him back in DC, but does anybody have any --

DR. MOULDER: I brought that one up and basically asked the epidemiologists were the studies similar enough that that would be easy to do and the answer I think we got is the Muscat study and the Inskip study are relatively similar in the design, but Hardell, the Swedish study is quite different.

DR. McBRIDE: I guess the second part of that answer is will we get new information or more precision out of doing it --

DR. MOULDER: I think it would help with some sub-group findings, because the studies were sort of done in parallel, different studies analyze different sub-groups, so you could at least say could we look at whatever definition we use for -- what was the sub-group of tumors -- all these studies might be able to use the same arbitrary definition of this sub-group and right now, what we have is slightly different arbitrary ones.

All of the studies looked at the longest induction time group they could find, but each one of those chose a slightly different definition.

McBRIDE: Yes.

DR. MOULDER: So, one study talks about five-year users and the other one talks about four-year users and the third one seven-year users.

It just seems to me that it would help give you some clues on the sub-group. Any sub-group that only shows up in one out of three, isn't going to be very interesting. Right now, in some cases, we don't know whether some of the sub-groups -- what some of the sub-groups showed in some of the studies, because study X just didn't happen to use that subgroup.

DR. OWEN: And people have also pointed out the possibility, sort of the other side of it, that because this is a group of things, it could be that there is a strong finding that is buried in the group because you haven't teased out sufficiently specifically what sub-type you are talking about.

DR. MOULDER: I don't really think there are enough brain tumor patients in this to do any really sophisticated teasing.

DR. GRAJEWSKI: Not only that, I think the differences in exposure metrics were also mentioned in detail as being discrepant. A pooled analysis may be possible, but somebody would have to do quite a bit of

work, I think.

DR. MOULDER: But a parallel analysis is by definition a little easier?

DR. GRAJEWSKI: Meta analysis, I don't believe you are taking the individual data. Pooled analysis says you find enough commonalities in the study that you can actually throw it in one pot and reanalyze. Meta analysis has few restraints.

DR. McBRIDE: Perhaps it's worth following up. It would take some work and it could be limited additional information, but maybe there would be some -

DR. OWEN: Okay. Good. Let's dive back into the exposure discussion and I will try and get back to the first comments that were made, where Greg brought up this morning the need for biological mechanism information or the fact that we don't have the biological mechanism information to really inform us about what the critical metric would be for exposure assessment. I don't think we got a chance to fully discuss that point this morning. Is the implication of that the need for biological work or for exposure assessment work or what were you thinking.

DR. LOTZ: Well, there are two aspects. One, I think ultimately you probably need some

laboratory work to help. For example, I think we have struggled with this, but if you had a finding that was consistent in the laboratory system, be that in vitro or in vivo, then I think you could challenge it with deliberately different metrics or characteristics of exposure. I don't think anything like that has really been done.

The flip side of that then, I think goes along with what Q. was saying. You try and be a little more comprehensive or a little more broad-ranging in the exposure information you gather, so if later we find out more about the most meaningful metric, perhaps you have that information contained within what you have got, even though you didn't know what it was ahead of time, because you have been more wide-ranging in gathering as much exposure information as you can.

Obviously, there are limitations to that, but --

DR. MOULDER: Is to follow it up. I think what that means to the epidemiologist's design of the study, is you have to be very cautious about not getting locked into an assumption of what the correct exposure metric is, but simply acknowledge that they don't know what it is.

There is I think the analogy to the power

DR. LOTZ: Oh, I think it's totally relevant.

DR. McBRIDE: I guess the way I look at it is it's only the lab studies that tell us something about mechanism. I mean, that is their purpose to identify those cell changes that could conceivably lead to cancer.

The way I look at it, I try to use the word metric to mean that exposure, that dose that is directly related to risk and that is what we don't know, because we don't the mechanism. So, I think I agree with Greg that there really are two questions here and that is to try to identify the metric, the relevant exposure is that directly related to risk and lab studies would be the most helpful for that.

And in the absence of that as we had with the power line studies, you need to capture as many different aspects of exposure or dose and those parameters that affect the variability as you can and some are person-based or user-based and some are in the technology and all those need to -- we need to do some characterization of that identification.

DR. BALZANO: If I could interject, that could also become almost a study in itself. This could

 be a study on its own.

DR. MOULDER: Finding a dose --

DR. BALZANO: No, exposure --

DR. McBRIDE: Exposure.

DR. MOULDER: Oh, exposure.

DR. BALZANO: Thank you. That would be the first thing to do if we could do it, but you might as well acknowledge that we are trying to find a candle in the darkness. That is our situation right now. We don't even know where the candle is yet. The best you can do is just touch the environment as much as you can. I mean, that is what you do when you are in the dark.

DR. MOULDER: Exposure assessment is a viable idea independent of the cohort study.

DR. BALZANO: Exactly.

DR. MOULDER: But I would also argue that it is absolutely essentially for a cohort study, but it is worth doing even if you don't do a cohort study.

DR. McBRIDE: I think what we are saying is that that is essential before one can start. The identification of a metric is not essential, but as you say, we may not find that for a while.

DR. MOULDER: But the day that somebody does find a metric, this data will be absolutely

invaluable.

DR. BALZANO: I am going to be a little bit optimistic now, that while the biological outcome is very difficult to pinpoint, we are dealing with dosimetric as space, time and energy -- the only parameters we are using.

DR. McBRIDE: Epidemiology says the same - person, place and time. Very simple.

DR. BALZANO: But the point is that again, there are some standards in the space because we got phantoms in which we can put measurements and you know from the device what you can get out of it. You record this as time, the way people go around town, the kind of exposure they get. I am not saying it is simple obviously. I am not trying to simplify it, but since you are truly in the darkness, it is easier to touch the environment from the physical point of view at this point than from the mechanism point of view.

DR. MOULDER: It is not that easy. Again, take the example of power line studies. We are 22 years into it and there are still entire studies that cannot be compared to each other because they have no dose metrics in common at all. And still in that field, there is absolutely no agreement as to what the metric is, so you can't even do meta analysis in that

because you moment you pick a dose metric, you automatically have to throw away two thirds of the studies because they didn't use that metric or anything that can be compared to it.

DR. BALZANO: But I am talking about the dose metric study. I am not talking about an epidemiology study. You can make a comprehensive dose metrics study independent of --

DR. MOULDER: Metrics. I agree.

DR. BALZANO: When your bank is empty, eventually you got to put something in the bank to see if you can bear fruit later on. And this probably is the first thing we can take to the bank and then there is IARC coming down the pike. This study would help us figure out what is going on and if later on there is a decision to have this substantial study, because if you are going to 100,000 subjects --

DR. MOULDER: It also helps other things. One of the big questions coming out now with the publication of the SAR information on new phones is the question --

DR. GRAJEWSKI: I have a follow-up question. Yesterday we alluded to the fact that there were phantom model data out there to a certain extent and since there are many other data bases or data

sources, how much of that information could be utilized in a complete or comprehensive exposure assessment? Obviously the data logging is de novo. It would have to be done from scratch or taken from the IARC information, but are there other data sources that can be used as is to help?

DR. BALZANO: As far as I know, since 1996, '97, the FCC has -- that is some of it. By being web based, they know.

DR. MOULDER: That gives you the variation between phones when they are at maximum power.

DR. BALZANO: Absolutely.

DR. MOULDER: And the variation in the head when they are at maximum power. It doesn't tell you what the typical power is and it doesn't really tell you anything about how people hold the phones, because in those phantom studies, the phone is held in the worst possible place.

DR. BALZANO: Or where they think the worst possible place is.

DR. MOULDER: Or where they think the worst possible place is. The worst possible place where it is remotely possible to hold the phone.

DR. BALZANO: It is pretty close to it, yes.

MOULDER: So what we really need here is information about what -- how the phones are actually held in reality as people are moving around and how the power levels behave in reality as people are moving around and getting shadowed, being in buildings and out of buildings and nobody seems to have ever done that. We know these things happen, but they are not really quantified.

DR. LOTZ: Well, I think it's fairly recent, John, that phones that can do that for us have been developed, so they haven't really been implemented yet.

DR. BALZANO: But this is really an opportunity. Before you think about serious epidemiology, the serious epidemiology should be preceded by some serious dose metric. With all these parameters -- we really should be able to sit around table with some expert epidemiologists and start sorting out what everybody thinks is the most important and as far as I am concerned, even the data collection should be automated. At the end of the day, the phone goes back to the base station and this information would happen. Put it on the computer and you run with it.

DR. OWEN: My understanding of the

 situation

-- trying address directly your question -is I think the data that Howard referred to that is in hand is more like bricks and mortar than it is a built foundation. I think there is a lot of work to using that available information before you would actually have something that you could build your epi study on. I think there is a big gap there.

DR. LOTZ: Yes.

DR. McBRIDE: One thing I feel is that the planning for a large study, say a cohort study, doesn't need to wait until there is a set of exposure studies. I think the two could be done in parallel.

DR. BALZANO: There is an important point that might come up, Mary, and that is if we found out that the phone doesn't mean anything, we would not have to ask what phone they were using. In other words, the phone washes out. What really counts is the amount of time you are using it and the environment you were using it. It could be that that is the case, in which case, forget about asking what kind of phone they were using. Verify that they use the phone for a period of time.

This can help. What I am suggesting is, yes, they can run in parallel, you are right. But I would give it a little bit of precedence to the

because that can help you formulate a bit better.

DR. MOULDER: But the reality is that if they decide to set up a cohort study, they don't need the information from the dose phones until they are ready to define the questionnaire and they have a lot of work to do before you get there.

DR. BALZANO: Yes, but before this questionnaire gets bolted down, it would really be rational to have the data from the dosimetric phase of the study, because then your questionnaire might be simpler or more --

DR. MOULDER: But it wouldn't stop us from locking in how you were going to recruit your cohort or even starting to recruit the cohort --

DR. BALZANO: You are right.

DR. MOULDER: There is a lot of work before the first questionnaire --

DR. GRAJEWSKI: Yes, it is a question you should see on the survey instrument, because if we sat down in a room and locked the door and some of you had in your minds a study design for the exposure assessment component, it would be possible to draft a questionnaire that incorporated all aspects of that.

But again, if you are talking about

administration of updates, you don't have that kind of -- it has to be an efficient instrument and then you are cutting down 10 pages of questions to about three questions that you can fit in on a 10-minute web update or whatever you are going to do and for that, the results of the assessment are needed.

You could write a very long exposure questionnaire with all possible questions.

DR. BALZANO: And the exposure parameters. You want to find your surrogates -- to the smallest,
yet most significant sets, so your questionnaire is meaningful.

DR. McBRIDE: Then it may be as you pointed out that other sources will give you better information, whether it's a card in the phone or transmission --

DR. MOULDER: I guess the real hope is that the dose phone data would simplify the questions you had asked. One thing I would really hope is right is that the phone model will wash out, so you don't have the track which phone people have. If you didn't
have to do that, it would make life a whole lot easier. We just don't know at the moment.

If I am wrong and the phone doesn't wash out, then it's going to be absolutely critical to know

not only that they had a Motorola phone, but exactly which one it is. And if you have to have that information, it's going to make the cohort study more difficult, but you might as well know that.

DR. BALZANO: That is exactly what I am saying.

DR. MOULDER: In fact, the information from the dose phone study could affect the cost of doing the study -- doing the cohort study -- assuming that the longer, the more questions you have to ask, the more it's going to cost you and the more people you lose.

DR. GRAJEWSKI: Then you have got to worry about the people that you have lost and there is a lot of -- you don't want to lose people. And if you have a 20-page update every six months -- yes, exactly.

DR. BALZANO: A two-page update would be the best bet.

DR. GRAJEWSKI: Ten minutes, yes.

DR. McBRIDE: One thing that was mentioned yesterday is the impact of changing technologies in terms of data gaps -- not exactly a gap, but it will be.

DR. OWEN: Good natural break. Shall we take 15 minutes?

 (Off the record.)

DR. OWEN: Okay, back to my notes. In very little time, I put bullets down based on where we were at the end of the day yesterday when we were trying to summarize discussions of potential prospective cohort study.

I would like to start actually again at the bottom of this list with the cost question that Q. raised this morning. I just wanted to make sure that I understood correctly that we are not going to put anything after that question mark this morning, but that if I follow up with people, Ken, of course, and other folks, that it shouldn't be too hard to ballpark costs on this for consideration.

Do I understand correctly?

DR. BALZANO: Let me make it a point to ask the epidemiologists here, suppose that you got 100,000 members in the cohort. I am talking about per year -- $10 a person? $20 a person, $30 a person? What are we talking about?

DR. McBRIDE: I really don't think I can give an estimate.

DR. MOULDER: Let's try a different question. What are the major costs of a cohort study? The costs of analyzing the PN, the cost of putting it

together, the cost of following the people?

DR. McBRIDE: Proportionally, the major cost is recruitment, because it usually takes multiple efforts.

DR. MOULDER: So that is a big up front cost.

DR. McBRIDE: And there is the loss rate at the beginning.

DR. GRAJEWSKI: Yes, the monetary incentives aren't even the big deal. That is minor.

DR. McBRIDE: No.

DR. GRAJEWSKI: It is the person effort in tracking people who drop out or --

DR. McBRIDE: Identifying them from whatever sources and then contacting them, getting their consent, getting them recruited. And controls are usually -- no, I am thinking of case control studies.

People from the general population are usually harder and more expensive to recruit than wellidentified case groups where there is usually a identified source that you can go to and there is more motivation so you get a higher initial participation.

So, cohort subjects are expensive to recruit. And in a cohort study, also as you mentioned,

 the follow up effort is expensive.

DR. MOULDER: How does the effort at the end when you analyze all this compare to the cost of getting going?

DR. McBRIDE: The lesser costs are the analysis and the data collection, although I would say the data collection is a sizable proportion in a cohort study because it is ongoing.

DR. MOULDER: Then what I picture -- we are talking about being arbitrary for a moment of a 10year study. If you write a 10-year budget, there is going to be a lot of money in the first two years. Then less money for a while and then another big budget at the very end as this is all gathered together and analyzed. No?

DR. GRAJEWSKI: I would just modify that slightly. Yes, you need money at the end for analysis, yes, you need money for start-up and for setting up the data systems and so on. The gotcha that has gotten us in our shop is tracing of individuals.

Now, that varies by study structure, but again, somebody has been with you for every six months and then suddenly drops in the eighth year or something like that, you have to try to find that person and despite what Ken was saying that -- certainly it's an

to know where that person was six months ago, you still have tracing efforts and it is surprising how people can get lost and that is contract person time to get that done, which can be very expensive.

DR. BALZANO: That's why I was trying to put almost a number per person per year, because you can average it out and multiply it by 10 and eventually, it boils down to something of that type. I am sorry I don't have experience with epidemiology. I got all my experience with in vitro study and in vivo studies. Epidemiology never happened.

Actually, the large epidemiology study by Motorola wasn't done by me. And it was extremely expensive, but I didn't control it.

But to try to pick a number right now, I would say somewhere between $20 to $30 per person per year?

DR. GRAJEWSKI: No, I think that is an under estimate.

DR. McBRIDE: Yes.

DR. MOULDER: The normal every six month follow up is fairly inexpensive. It's when all of a sudden the person disappears off your radar screen. Did that mean they moved? Does that mean they died?

DR. BALZANO: I said per year and then you

have to multiply it by 10 to get the entire expense per person.

DR. McBRIDE: I think rather than try to put a price on it, I can think of several studies and I know Ken and Peter can, too, that are similar in design and can give some estimate. That is one way to do it. There are the ones we know of -- the nurse's health study, but there is also -- I don't know how appropriate these are. They are child health studies.

DR. MOULDER: Are your colleagues open to telling you what such and such a study actually cost? DR.

McBRIDE: I don't know. In Canada, it would be no problem. Here, I don't know.

DR. LOTZ: I think particularly those studies at certainly our sister agencies have done is public information, so it's not difficult to get that once you know what you want to ask.

DR. McBRIDE: In terms of tracing them, you can do a lot of things. In the US there are files that are not publicly available, but can be used by researchers.

DR. GRAJEWSKI: There is Social Security Alive, there is a number of them.

DR. McBRIDE: But they all have a cost. DR.

GRAJEWSKI: Yes, and if it comes down

 the last resort, the credit bureau, you talking about $400 an hour online. These are not cheap methods.

DR. BALZANO: Remember, $30 per person per year is three million dollars a year times 10 is 30 million dollars.

DR. GRAJEWSKI: I would guess that is somewhere in the ballpark.

DR. BALZANO: Somewhere, I am trying to put a boundary on what we are trying to do. I mean, that is what we are suggesting. Something that is -$30 per person per year is three million dollars a year. You are not talking change.

DR. McBRIDE: The diet and breast cancer prevention study, which might be a comparable type of study, I think NCI is sponsoring that. I know Seattle is one of the sites and we are also and it's 10 years following people in the same kind of age range that would be talking about, but following women rather than men, so that mobility and tracing may be a little different, but it's the same and it involves periodic data collection.

DR. LOTZ: I was going to say, Mary, that was one thing and I only know the details about one segment of it, but the Hanes study involves a lot of actual subject testing, so I am concerned that it

wouldn't be a very good model, because you are employing technicians at multiple sites fulltime to bring people in and actually do rigorous testing of various protocols.

DR. McBRIDE: Yes.

DR. LOTZ: And that has got to be a lot more expensive than the kind of information gathering.

DR. McBRIDE: Of course, we don't have the protocol for a cohort study. At some point, that might be a component, but I would agree with you that that would probably be different.

DR. LOTZ: You might be able to parse out those differences and say -- they need this much and the other parts need this much, but there is a lot there that is probably more complex.

DR. BALZANO: I find myself very often in these situations with people coming for a research project and I got put a boundary in front of my manager -- otherwise they throw me out of the room. But remember, every time you add the $10, it's X million dollars.

DR. GRAJEWSKI: We can make cost estimates, but I think Greg's point is really good in that is that my basis is on the basis of bio-monitoring studies and I know what types of

costs are involved

there. This isn't that. It's web based and there are cost associated with that and with follow-up, so it's finding the right structure and I think if we find some similar studies, it will be a fairly simple comparison as you were saying.

DR. OWEN: I was wondering -- Q. and some others have mentioned the possibility of using the technology in as many areas as possible and I guess since it's not been done, not be optimized, you might not be able to answer this, but can anybody guess what affect it might have on the cost for instance of tracing drop outs and other things? It is anticipated that somehow using the technology on all the subjects might reduce these tracing costs since we figure most or all of the subjects will be subscribing to wireless devices?

DR. McBRIDE: We can phone them I guess. DR.

BALZANO: Use the phone.

DR. LOTZ: Actually, I would think, Russ, that that almost could be part of the tracing problem because I think at least my sense is that people in the US change companies a lot and so all of a sudden they are going to drop out of sight from the contact that you have.

So, I am not sure that it offers an

advantage.

DR. MOULDER: The big advantage is going to be routinely following up the people you can find. Once you lose them, it's old fashioned detective work.

DR. LOTZ: People are with Verizon now and then they see the ad and go, oh, that is a better deal, I will go there. My sense is that people do that a lot.

MS. BASILE: Yes, we have a fairly high churn rate.

DR. McBRIDE: I wonder if people change their e-mail addresses quite so frequently though and that would a second --

DR. MOULDER: They learn not to.

DR. LOTZ: Yes, there is so much disadvantage to that in terms of having what you want e-mail for is people to get in touch with you, that I suspect that -- more stable.

DR. BALZANO: Again, though, what Greg was saying is correct, but I think that the market is stabilizing in the sense that a lot of these other companies are being merged. There has been a consolidation of the industry. In that past, that is correct, but going forward it might be less so because there are fewer providers.

MOULDER: The initial question is if we do it web based, where is the savings? I see the big savings in routine follow-up and possibly in recruitment and maybe it will make your life a little easier at the end because since the data came in on a web, some of it, we won't have big coding -- whoever the we is -- cut down the cost of the coding.

DR. McBRIDE: In terms of data clean up and data editing and data manipulation, that could be much more efficient. I would agree with you, that and a cost of follow-up will probably be considerably reduced.

DR. GRAJEWSKI: It's like a selfadministered CADI computer questionnaire and the data comes directly to you. The caveat there is you have got to make absolutely certain before this thing goes real time that people understand exactly what is meant and the questions are good beyond the pale.

DR. MOULDER: Pre-testing --

DR. GRAJEWSKI: Oh, sure, sure, but I mean more so for something like that because there is no -it's not face to face. You don't have the opportunity to post field code and say this was what was meant, we can interpret that. So, if you have a loser question there, they are going to come rolling in you won't have

 -- the interpretability of questions will be lost if you have something that is not worked out. So, it's all the more acutely important.

DR. BALZANO: But you would pre-test it anyway substantially.

DR. GRAJEWSKI: Yes, even more so than a face to face.

DR. BALZANO: You would pre-test it to accuracy to the hilt. There are ways to put some prevention in the process.

DR. MOULDER: So, I hear more than a million and less than 100 million?

DR. BALZANO: I would say more than a million. Certainly more than 10 and less than 100. It's somewhere in there.

DR. MOULDER: And contrary to my initial thought, except for a little bit of front-loading, that is spread kind of evenly across the 10, 15, 20 years that it is going to go.

DR. McBRIDE: I don't think so -- I don't know if you would agree with me, but the ongoing data collection and the tracing and the follow-up issues will cost continuous --

DR. BALZANO: A lot of animal studies go that way also. You got to set up and there is a lot of

front-loading and then there is a period where nothing happens. You just feed the animals. Then there is the enormous amount of --

DR. LOTZ: Except for paying all your staff to feed the animals every day.

DR. BALZANO: No, no, that is a constant expenditure.

DR. GRAJEWSKI: You are feeding the animals. You are not chasing them.

DR. BALZANO: Eventually, you end up with a back end, which -- my projects were front-loaded and back-loaded and when you average out, you can almost get what each animal is going to cost. And this is dealing with an animal obviously, not with a higher level animal.

DR. LUNDQUIST: Since we are talking prospective studies here, I would like to say something, if I may. Yesterday during a break, I talked to somebody who has been here both days and I discovered has some interesting and I think important observations to make.

Her name is Laurie McClung and she works for Baldwin Reporting and she is making the record of our meeting here. She had been interested in what I said about the lengths of the conversations being

 important

and she pointed out that there is a population consisting of young kids -- I gather high school and college age, late teens and early 20s, who tend to get cellular phones and talk for long periods of time to their friends all over the country because there are no roaming charges. Their parents pay the phone bill typically and get some idea of how much talking is going to by the size of the phone bill and if there is, as I suspect, a hazard associated with duration of continuous uninterrupted use of the phones, this would be a population particularly at risk.

She then pointed out this would probably make a very poor survey population because these kids are not going to want to sit still and be surveyed, respond to survey questionnaires, and that is right. I think there would be difficulties, but then I got to thinking, no, we do have another very interested party here who would be willing to sit still and that is the parent who pays the bills and has invested in this kid.

We are talking now about kids -- over $100,000 the cost of rearing a child and they are paying these phone bills as well and if my suspicion is correct, people who do have these long exposure are going to be excellent candidates for early on-set Alzheimer's. Can you imagine what congressional

might be like in 10 years if there is an organization of angry parents who have spent all that money to launch their kids for successful like, only to find that their brain is going, they are being diagnosed with senile dementia and they are candidates for going into nursing home in their late 30s?

DR. LOTZ: I think, Marjorie, the problem there -- and we did talk about that a little yesterday -- the problem is latency there. You are talking about a 30-year study.

DR. LUNDQUIST: For cancer, yes. I am not so sure for Alzheimer's.

DR. LOTZ: I would say the predominant mode of that use is young teens, not older teens.

DR. LUNDQUIST: You think 12, 13, 14?

DR. LOTZ: Yes.

DR. LUNDQUIST: Well, why don't we hear from Laurie? I believe she is a parent.

DR. OWEN: Actually, though I think that that fits more in where we were talking about the importance of assessing all the parameters that affect the exposure or the dose and that is part of usage patterns, which has a clear influence and so if there is study in that area, I do think that that is one thing you want to keep into account. Not only figuring

 the usages patterns of 45-year old executives, but everybody else, too.

DR. McBRIDE: I would add, too, Greg's point along latency applies as well to Alzheimer's, s cancer. Both have an average age at diagnosis at well over 60.

DR. MOULDER: Is there any precedence for having kids in a long cohort study?

DR. GRAJEWSKI: Yes.

DR. McBRIDE: I guess point I was trying to make is that we will get an answer to that question more quickly by studying those people who are closer to that average age at diagnosis of Alzheimer's, by looking at a cohort that is older, looking at exposure and following them for a reasonable time. If we start now with teenagers, you are right -- they are terrible subjects to follow, to participate in a study, but we wouldn't get an answer for 50 years.

DR.LUNDQUIST: I am not so sure that is true though.

DR. McBRIDE: But one needs evidence before --

DR. GRAJEWSKI: To my understanding there is a very large longitudinal study being started up and I think it's NIHS and some other federal agencies.

 There are planning meetings going on and this is a large longitudinal study of growth and development, a very, very cohort of children -- I believe it's somewhere around 20,000. There are groups forming to look at the various things to be studied, questions to be raised. So, the effort is in its starting stage.

But it focuses on child growth and development over a long period of time and I suspect exposures of this sort would be included in those that would be studied. I would be almost positive.

So, I believe that not only the latency questions, but you really need to define the age range of the group you are going to study and if you try to do everybody in one study, you will have a lot of inefficiencies, loss to follow-up and other problems that you wouldn't have if you sort of targeted on one age range.

DR. McBRIDE: There is also the UK child health study, which is a similar kind, taking a large cohort from the 90s, called Children of the 90s looking at exposures such as this.

So, in terms of broad cohort studies, there are those already going on.

DR. OWEN: I guess the one other thing that comes to mind is if -- there has been a lot of

discussion of using the web based approaches for the recruitment, partly because that would be the intent to use it for the data collection and you might -- unless you make efforts otherwise, you might end up sort of heavily -- ending up with a lot of recruits that are in the younger age categories just by virtue of the fact that they either have more time or more access or didn't have to deal with adapting over to using the web all the time from using something else.

DR. McBRIDE: Just to follow up a little bit more, I think the most feasible study that might come from looking at adolescents is a type of clinical type of study looking at a short term effect such as cognitive function. That way you can assess effects using a smaller group of volunteers or whatever. I think that would be feasible to do and identify those kinds of problems.

DR. OWEN: Then again, at least my reading of some of the things coming out of the UK work over the last year or two is consistent with efforts to get that kind of study included in their program as well.

DR. MOULDER: That is also another place where animal studies would come in. If you do believe that there are striking age-dependence of the facts, it's a whole lot easier

to do that with an animal.

BALZANO: At least to get some --

DR. MOULDER: Yes, whether there is something going on --

DR. BALZANO: A good animal study should precede before you undertake an effort, because tracking the kids is going to be -- plus they are very valuable --

DR. McBRIDE: I mean, you have to start with the premise that that age group has something very different in their brain function or brain development than someone somewhat older. It's easy to identify them as a special population, but on what basis? For childhood leukemia, it was more obvious that looking at children one to four years of age was important because their immune systems are still developing after birth and there is some reason to think that immune system function and cancer susceptibility might be related.

And certainly, adolescents are changing. There are several physiologic systems that are changing, but it's not as obvious that they are more susceptible in terms of that age group -- brain function and those issues, but certainly short term outcomes could be examined.

DR. OWEN: We have still got about 45 minutes and I am glad to be able to get a lot of extra

information on that cost question.

As I said, in a very crude shorthand, I tried to recapture basically the list that Ken reeled off yesterday afternoon. The top part is what he was saying, why would you want to do a prospective cohort study. He mentioned to characterize the exposure prospectively and periodically because it can change over time.

DR. BALZANO: Technology changes over times.

DR. OWEN: To be able to assess multiple outcomes, which as has been discussed, can mean outcomes that you didn't realize you needed to look at until later on.

Of course, to be able to address questions related to longer induction times and the ability to perhaps better target a population that has higher exposures than so-called general population.

Does that look in broad terms comprehensive for the whys?

DR. LOTZ: I didn't write them down, Russ, but I recall him talking about five points.

DR. OWEN: Oh, diversity and use of -- of course, we will be able to get it from the transcript. He had characterizing exposure prospectively and

characterizing it periodically as two points and I put them as one. I think that is what it is.

And actually the last one there on the bottom is the only comment -- the cost -- is the only comment I think I heard when I said let's turn to question to why not a cohort study. And I think that was the only comment that people brought up.

DR. GRAJEWSKI: There are a couple of methologic things which I think are not as pertinent to a wider audience in terms of advantages and that is the direct estimate of risk rather than estimation through an odds ratio or retrospective estimation and then the reduction of certain biases, which are attendant to a case control design. Those are advantages, but they are more methologic. He's got the main ones here.

DR. BALZANO: The only thing I can add is to recruit only the eager volunteers. You made the point that in this type was a really sincere blend in technology and you should be able to get people who are really interested and will stick to it. That was additional, the only thing that was an additional comment.

DR. McBRIDE: I think I would broaden that to say that it's critical to get high participation and data completeness -- compare case control to

prospective methodologies.

DR. MOULDER: I asked a side question here because I didn't understand and maybe it is relevant and that was if cohort studies had all the advantages, why does everybody do case control studies and the answer was because they are expensive and long. And that is the down side to this.

DR. McBRIDE: And you can lose participants and lose information over time and --

DR. MOULDER: So, cohort studies, to be quick and dirty, are better, but a lot more difficult.

DR. GRAJEWSKI: Right, and if you are looking for a specific outcome, a very specific histologic -- a tumor, whatever, you have got to find - you have got to make a big hay stack to find that needle, so that is a design element, but it is a better study structure certainly.

DR. McBRIDE: The other thing probably that should be mentioned is we may not be able to look at rare outcomes even with the cohort study this size.

DR. GRAJEWSKI: Right.

DR. MOULDER: I don't think that is really a disadvantage, because right now the concern is not that there are rare outcomes. The concern that is out there is that there might be a major hazard.

DR. McBRIDE: Well, I am mentioning it. DR. LOTZ: That depends on which one you call rare. I mean, brain cancer is rare.

DR. MOULDER: We are talking about a study the way I heard Ken come up with 50,000 subjects, which should be big enough over a 10, 15 period to detect a doubling of brain cancer rates without any trouble if that was occurring.

DR. GRAJEWSKI: If that is what you want to do. If the exposure assessment goes forward and animal studies go forward, and you have a specific biological hypothesis for specific histology, you may not have the power to catch it, catch that particular - you may see an increase in brain cancer, but there may be something that you are missing and that would be a tremendous frustration at the end of 10 years.

DR. BALZANO: But knowing the number of members of the cohort, normally you can make a forecast on that power of the study and the confidence level of the various outcomes.

DR. GRAJEWSKI: Right, but that is still a guesstimation. A big one.

DR. MOULDER: It just seems to me that we don't really want to make that criticism because this study is big enough. As Greg said -- I mean, brain

 cancer is something I consider a rare disease. What this is -- not enough power to pick up something very rare.

DR. McBRIDE: Well, let say like neuroepithelial brain tumors, which is a sub-group of the brain cancer population -- if we are looking at that, there would be pretty wide confidence intervals -

DR. MOULDER: But if you really thought they produced a specific sub-type of brain cancer, I think you would be driven to a case control study. Only something like 100 cases of that type of cancer per year.

DR. OWEN: Well, that will be the question that will be raised when we get the IARC results -each of the IARC results.

DR. McBRIDE: Yes, a large case control. DR. OWEN:

Okay, so then the rest of what he listed then was sort of under the characteristic of potential optimal features and when I said -- well, I think he did say 50 to 100,000 --

DR. BALZANO: That is exactly right.

DR. OWEN: I remember when he was trying to get the lowest and he said what if we had 25,000 that were sort of going to be in the high end --

BALZANO: But then you can point out 50 heavily exposed and 50,000 low exposed. That was the maximum range.

DR. OWEN: Right, but I think in that comment he was trying to point out how nice and small this cohort study could be -- in comparison to his most recent experience in this area.

DR. BALZANO: By doubling the members of the cohort, again the possibility of catching the rarer tumor should go up.

DR. GRAJEWSKI: Go up, but not necessarily enough.

DR. OWEN: Yes, I think the flip side of what we were just discussing was that if you had either information from cohort or other case control studies or laboratory studies that indicated a specific end point, a rare but specifically identified end point, then the case control is the way to go to maximize your sensitivity and at the same time, you are minimizing cost.

DR. BALZANO: Right now I thought what we were looking at is the long term potential induction. That was the reason to go down this path, is to catch long term induction issue --

DR. GRAJEWSKI: That is another advantage,

right.

DR. BALZANO: Because I think that was the number one issue that we were trying to deal with.

DR. MOULDER: Plus the fact that we are fairly confident that somebody else is doing a big case control study.

DR. BALZANO: The point is that this is what is missing. Finally, that was the conclusion yesterday. How -- if we are trying to fill a hole, this is the hole that is missing right now.

DR. McBRIDE: I guess I think of it differently. I think case control studies of cancers with long induction studies, in theory can be better because you don't have to wait. You have already got the end point.

What is missing is good exposure assessment in the past, from the past, and outcomes that you didn't think about or that you can't include.

DR. MOULDER: Also the fact that we don't have exposures 20 years ago.

DR. McBRIDE: Yes.

DR. BALZANO: That is what she said.

DR. McBRIDE: We don't have exposure assessment and data from the past.

DR. MOULDER: You are saying no good

and I am saying we also don't have exposures 20 years ago. We didn't have people using the phones in appreciable numbers.

DR. McBRIDE: Yes, but if you start -that's true, but if you started the case control study 10 from now --

DR. MOULDER: You would still have lousy exposure --

DR. McBRIDE: Yes, you have lousy exposure assessment and you only have a limited number of outcomes to look at. I mean, a cohort study from cancer, which has a long induction period is expensive because you have to follow subjects for so long. If you are looking at a disease with a shorter induction period, it's much more feasible.

But what you get is much better exposure assessment and the possibility of looking at multiple outcomes and we have so little biological data to guide us on what outcomes to look at, so that is what I see.

DR. BALZANO: So, this is the wider net. DR. McBRIDE: Yes.

DR. BALZANO: If you are in the dark, this is the wider net if there is a fish.

DR. MOULDER: One thing missing from this was the suggestion I think from both Mary and Ken that

this should focus on older users who are closer to the time when they are going to get these various diseases --

DR. McBRIDE: Yes, and young enough to have a reasonably high prevalence of cell phone use.

DR. MOULDER: But I don't know that anyone ever defined what that age range was that you wanted. But it's not all ages that you want.

DR. McBRIDE: No, it would be --

DR. MOULDER: What?

DR. McBRIDE: What does the IARC study -DR. OWEN: Ken posited emphasizing the middle age. The people who were just before when you start to see high incidence --

DR. LOTZ: Thirty-five to 50?

DR. BALZANO: I remember a number of 40. DR. OWEN: Yes, he said 40 and older or something like that.

DR. MOULDER: I think that is a point worth listing on the primary list of characteristics, yes.

DR. GRAJEWSKI: Now, on that fourth bullet down, the baseline screening, you are actually describing two activities. If you are doing this completely on the web and interacting on the

web, there

does have to be some initial screening questions and then beyond that, if you pass that hurdle, you would be going into a baseline questionnaire, which would collect your baseline data for people who were going to participate in the cohort study. The screening would basically shutout your teenagers or whoever else --

DR. MOULDER: Of if you decide you have to limit it to the US and North America --

DR. GRAJEWSKI: Right. So, it's really a two-step process there.

DR. OWEN: So, it screening and collection of history.

DR. GRAJEWSKI: First screen. If you make it through the screen, you collect the baseline questionnaire and then you hit them with updates every six month or whatever.

DR. OWEN: I reiterate exposure assessment here, but we basically covered that as a whole separate topic and actually talked a fair amount about it today. I think we talked a fair amount about the modern technology, the things it would do for you in terms of possibly looking at other agents or exposures, I guess is the better way to look at it, but also as a tool to reduce bias and increase recruitment. I am not sure if I fully understood how it increased recruitment, but --

 DR. LOTZ:

I think the idea there, maybe, Russ, was a little bit to put it crudely, not that we want you in the study so we can see how we fry your brain, but rather we want to investigate the possible health outcomes of using modern technology, so it becomes a more appealing study.

DR. OWEN: Because it's not frightening. DR. LOTZ: Yes.

DR. BALZANO: Because it's not only the cell phone. If you remember, we talked about the modern technology in society and these are people who interested in technology. They use the screen. They use the web.

DR. GRAJEWSKI: That is a commonly used -in other venues, you bury the questions of interest within a matrix of other questions that are either not as threatening or relevant in some way. It is a trade off with time and effort on the survey instrument. If you put in too much of that stuff, you are going to lose people just from how much there is to go through.

DR. McBRIDE: I guess it goes to the point that public concern is often raised more by the fact that a technology is new or not understandable to them than actual evidence for harm and this is one way to address public concern. To be able to say one is

proactive, one is actually investigating --

DR. MOULDER: So, this would also help if for some reason this drops off the public's radar screen half way through the study. You include other things that are on it to keep people interested. What happens if people stop worrying about this in five years and we start losing people? You have to worry about that?

DR. McBRIDE: I guess, the whole idea of getting committed participants in the beginning, in the broader hypothesis is that people don't drop out because all of a sudden they are less concerned with one aspect of it.

DR. GRAJEWSKI: The volunteer bias here is toward a group of people -- I can't remember who named them that, but the worried well. Remember that? And these are people who are intensely engaged in their health and well-being and in this case in technology and doing a little diversification in that way does speak to shoe concerns and those interests.

DR. LUNDQUIST: I do see a pitfall that I would like to call your attention to. No question that a prospective study looking at the health effects of various new technologies would be good to do and would be a lot less threatening to people who want to

participate. The problem that I see is that if these technologies are going to include not only the use of cellular phones, but also the use of various things like computers and other electronic devices as it almost certainly would, you run into the possibly, which I think is not a possibility, but a reality, that you could get the same general type of health effects from different sources and this, if you weren't aware of it, could really lead to misleading results when you start to evaluate the data.

For example, if exposure to this technology and that technology both produce a common health effect, it may be a little hard to say is one of these causing it or is the other causing it or if you knew this one was causing it and you didn't know that one was causing it, you could totally misinterpret it.

DR. OWEN: Combined exposures to different agents is a very important topic and usually wellconsidered in study design. The other thing that comes to my mind along with what you are saying is that presumably everything we said about exposure assessment for wireless phones would apply to what we would want to know about RF exposure assessment from another RF device.

So, when you are doing an epi study, you

 want all your aspects of exposure assessment to be strong and if you are including other modern technologies or other exposures in your study, you are not just doing it as a smoke screen. You do want to know what those exposures really are. You are not just going to have these questions in there that you are going to throw out.

DR. GRAJEWSKI: Absolutely not. I wasn't implying that.

DR. OWEN: I think that covers what you are saying on two counts.

DR. LUNDQUIST: You are quite right. Other RF sources could produce these similar things. However, the big reason I mention this is power lines, as far as I am concerned, are an RF source that have not been recognized as an RF source so we are getting RF diseases from it that everybody for 20 years has been trying to correlate to ELF fields when the correlation exists, but it's not a causal relationship. So, I see heavy potential for gross misinterpretation of the results from this kind of study if you are exposed to fields that are associated with current carrying wires, which includes computers, plus a whole host of other things.

DR. LOTZ: Marjorie, I would say that

actually argues for the broader approach, because --

DR. LUNDQUIST: Oh, I don't think it's a bad idea to do this, but I see pitfalls with our current level of knowledge.

DR. LOTZ: What I was thinking was the pitfalls are worse if you don't start out to cover this wider net, because then you might not even account for them at all.

DR. LUNDQUIST: I'm not saying you shouldn't do it. I'm saying that I prepared these second comments that I handed out because I didn't feel that people really understood what I was saying yesterday and I have a feeling that five years from now, I will still feel that people are not hearing and understanding what I am saying. It takes a long time for a radically new idea to really penetrate. That's all I'm saying.

DR. LOTZ: Well, that works both ways. DR. McBRIDE: I guess I would agree with your arguments for including the broader technologies. Certainly that was something that was done in the ELF studies that I was aware of, other sources of power frequency fields.

Another issue that has come up is the modulation at the power frequency of RF devices. There

are ways to analyze the data, as you point out, to deal with these different aspects of exposure.

DR. LUNDQUIST: Speaking of data, I have observed in my historical studies more -- I don't quite want to use the word deceit, but I have seen more effort to concern or to prevent a certain interpretation of data getting into the literature.

DR. OWEN: That is an interesting topic, but I think it's getting off scope and we don't -- we only have 20 minutes left.

DR.LUNDQUIST: But I want to know, are these data going to be publicly available?

DR. OWEN: That is an outside issue and I think I addressed that yesterday in discussions.

What I wanted to point out just to finish up the issue that you raised though before that, was that I think that it is consist with sort of general good practice to try and include these. For instance, when the NCI was designing its lymphoma study, we went down there and said try and do something to capture

cell phone information, so they tried to add something. That was a while ago. How well they were able to do that in that study is questionable.

What I am saying is when you sit down and are actually designing the study, you will probably say

 what do we know today about -- or what don't we know about power line related exposures?

DR. BALZANO: I know power line related exposure is just about myth. You can go out in middle of the Everglades and you find it. By now, it's almost exposure you get from the air.

DR. OWEN: Well, depending on what you decide the metric is.

DR. BALZANO: Yes, I was surprised. I got int middle of Everglades and I got a reading. Eventually, it's gets into the background and that is a big part of your background noise. I am not saying that it is, but eventually it might get there. That is one of the disadvantages of modern technology.

DR. OWEN: A general note, I wanted to point out and Ken mentioned this yesterday, that because this is a prospective cohort study, we are not trying to nail down all the design features and that it would take a lot ore work. So, obviously we can't be too comprehensive at this stage.

But there was sort of a separate point that I put as a bullet here that not only did I sense that people felt there was a lot of importance to very solid and extensive preliminary or initial work in the exposure assessment area, but also that there were a

 lot of other sort of pilot areas of work in terms of developing the right instrument. It's assumed that at the beginning of the study, you would be building in measures, quality control measures. You wouldn't be making decisions about is this the best instrument or is the web access going to work for data collection or how well is it going to work for data collection.

At this moment, I can't think of an area that is directly related to our area today that we haven't touched on yesterday or today.

AUDIENCE MEMBER: Can I just make one comment? You concentrate a lot on the exposure assessment up front in terms of doing something very rigorous. Obviously that is going to look at today's technologies. If you are talking about a 10, 20 year study, you are probably going to have to do that again at different points in the study, because per that thing I showed you there, how and what we use for wireless communications is probably going to change rather drastically during that period and I think we should capture that, that it's not just a preliminary assessment, that you are going to have to have equal points in your study that you may have to go back and re-look at the assessment or the devices and what people are using.

BALZANO: The exposure assessment should be reassessed for the major shifts in the technology. You are right. Otherwise, it's not going to make any sense.

DR. LOTZ: I think that came into that first bullet on doing it periodically.

DR. MOULDER: You have to worry about changes in technology and changes in how people use it.

DR. BALZANO: The technology will drive how people use it. If you give them a screen, they are going to use it.

DR. OWEN: Yes, that is important to emphasize.

DR. BALZANO: Okay, do you remember Michelangelo?

DR. OWEN: Yes.

DR. BALZANO: When he made a major piece of work, he used to go this big quarry of marble and pick out a piece of marble and that is what you have done today. You have a block of marble. But it is a good block of marble though.

DR. OWEN: Now we are trying to peer inside.

DR. BALZANO: Michelangelo would always say I know exactly where the statue is, but you got to

with a good block. I think you got a good block of marble. Now it's going to take a long time and a lot of sweat and tears.

DR. OWEN: Now, Abiy and I have to carry it home.

Well, good, I think then that we can close this meeting now. We own the room for the rest of the day, but I am planning on leaving pretty soon because I have a plane to catch and I think most people do.

Thank you all again.

(Whereupon, at 10:40 a.m. the meeting was concluded.)

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REPORTER'S CERTIFICATE

I, Laurie McClung, reporter, hereby certify that the foregoing transcript consisting of 78 pages is a complete, true, and accurate transcript of the meeting, held on April 19th, 2001 at the Regal Cincinnati Hotel, Cincinnati, Ohio.

I further certify that this proceeding was recorded by me, and that the foregoing transcript has been prepared under my direction.

Date: May 4, 2001

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Official Reporter

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